

Long-term outcome of combined valve repair and maze procedure for nonrheumatic mitral regurgitation

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Objective: The long-term outcomes of combined mitral repair and maze procedure for patients with nonrheumatic mitral regurgitation and chronic atrial fibrillation were evaluated.

Methods: Between June 1992 and December 2008, 187 patients underwent a combined mitral repair and maze procedure. The mean follow-up period was 7.4 ± 4.3 years. Chordal reconstruction was performed in 69 patients, leaflet resection in 91, edge-to-edge leaflet suture in 30, and ring annuloplasty in 156. In addition, a cryo-maze procedure was applied in 110, and a Cox–Kosakai maze and radiofrequency maze were applied in the others.

Results: There were 2 operative deaths and the 15-year survival was 71%. The 15-year freedom from greater than grade 3 mitral regurgitation was 61%; rates of freedom from heart failure (New York Heart Association class \geq III) and reoperations were 79% and 91%, respectively. Cardiac function was improved and left ventricular size was decreased significantly postoperatively. Multivariate analysis showed that a large left ventricular diastolic diameter (≥ 65 mm) was an independent risk factor for recurrent mitral regurgitation. Eleven thromboembolic episodes (0.79%/patient-year) were detected during follow-up examinations, of which 7 occurred in patients with recurrent atrial fibrillation. Sinus rhythm was regained in 86% after 6 months and in 63% after 15 years. Multivariate analysis showed that a small-voltage f wave was an independent risk factor for AF recurrence.

Conclusions: A combined mitral valve repair and maze procedure provided low rates of morbidity and mortality and led to well-preserved cardiac function. Left ventricular diastolic diameter and f-wave voltage can be accurate predictors of good long-term outcome. (*J Thorac Cardiovasc Surg* 2010;140:1332-7)

A mitral valve repair operation has become standard for nonrheumatic mitral valve regurgitation (MR), and recent reports have shown satisfactory midterm to long-term results, including freedom from reoperation and severe MR.¹⁻³ However, for yet unexplained reasons, in some patients who undergo the procedure the mitral valve does not remain competent.³ In addition to the pathophysiology of MR, ring annuloplasty, and preoperative heart failure status, persistent atrial fibrillation (AF) has been suggested to affect the long-term clinical outcome and durability of mitral repair.³⁻⁷ On the other hand, preoperative AF is reported to be a marker not only for surgical risk, but also for late adverse cardiac events and stroke; thus, sinus conversion is an important strategy for patients with AF, who are estimated to comprise from 30% to 40% of all patients who need a mitral operation.⁷ Therefore, a maze procedure is as important as mitral repair to achieve a good long-term outcome. Patients with persistent AF tend to have a longer history of congestive heart failure and may

benefit greatly from a combined mitral repair and maze procedure. We analyzed long-term outcomes of patients who underwent combination therapy consisting of mitral repair and a maze procedure for nonrheumatic MR and persistent AF.

METHODS

Patients and Assessment

One hundred eighty-seven consecutive patients (mean 62 ± 11 years old, 70% male, mean body surface area 1.58 ± 0.17 m²) who underwent a combined mitral repair and maze procedure for MR owing to nonrheumatic etiology and persistent AF from June 1992 to December 2008 were studied retrospectively. One hundred one (54%) had New York Heart Association (NYHA) class II congestive heart failure, 60 (32%) had NYHA class III, and 26 (14%) had NYHA class IV symptoms.

MR was assessed by color-flow Doppler ultrasonography, with the severity graded as none (0), trivial (1), mild (2), moderate (3), or severe (4). All patients had moderate or severe MR, and its etiology was anterior leaflet prolapse in 53 (28%), posterior leaflet prolapse in 75 (40%), both leaflets in prolapse in 33 (18%), and annular dilatation in 27 (14%). All patients were in persistent AF rhythm. The average AF duration was 3.5 ± 4.1 years and the duration was longer than 10 years in 15 (8%) patients. The height of the f wave in V₁ of the 12-lead electrocardiogram was less than 0.1 mV in 25 (19%) patients. The preoperative average left atrial (LA) diameter was 60 ± 11 mm and greater than 70 mm in 15 (8%). In all patients, the preoperative average left ventricular (LV) diastolic and systolic diameters were 63 ± 4.6 mm and 36 ± 8.5 mm, respectively, the average fraction shortening was $35\% \pm 8\%$, and the average peak tricuspid regurgitant pressure gradient was 35 ± 14 mm Hg.

Procedures

Appropriate repair techniques were directed to specific structures of the mitral valve (Table 1). Leaflet resection such as a quadrangular or triangular

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Abbreviations and Acronyms

AF	= atrial fibrillation
LA	= left atrial (atrium)
LV	= left ventricular (ventricle)
MR	= mitral regurgitation
NYHA	= New York Heart Association

resection was used in 91 (49%) patients, chordal reconstruction such as replacement with artificial chordae⁸ or chordal transfer was used in 69 (37%), and edge-to-edge repair, applied only to commissure lesions, was used in 30 (16%). A ring or band annuloplasty was performed in 156 (83%) patients. The ring annuloplasty was applied regularly in the later years, although it was not applied to every patient for the first several years in our series. A cryo-maze procedure was used in 110 patients (59%),⁹ a Cox or Kosakai maze in 69 (37%),^{10,11} and a radiofrequency maze in 8 (4.3%). The different types of maze procedures were selected by different time eras, because the procedure became less invasive with time. The cryo-maze procedure is the least invasive among the Cox, Kosakai, and cryo-maze procedures and it is the current procedure. Radiofrequency maze, which modified the energy source simply from liquid nitrogen to radiofrequency, was discontinued because of the uncertain transmuralit. The Cox maze was performed with a cut-and-sew technique. The Kosakai modification switched cut-and-sew to cryoablation on the lines from the right atrial free wall to the inferior vena cava, from the left upper pulmonary vein to the LA appendage, and on the extension lines to the mitral and tricuspid valves.¹¹ It also ablated the line from the right atrial appendage to the foramen ovale instead of the line of the intra-atrial septum to the foramen ovale, and stopped to ablate the line to the superior vena cava.⁹ It also preserved biatrial appendages that were cut out in the original Cox procedure. The cryo-maze procedure simplified this method further, and the only lines to cut were the right atrial free wall and right side of the LA, which had to be cut for tricuspid and mitral valve surgery. The cryoablation lines were the lines to the inferior vena cava and tricuspid annulus, the intra-atrial septum to foramen ovale in the right atrium, and box lines encircling bilateral pulmonary veins and lines to the LA appendage and mitral annulus in the LA. Radiofrequency maze was performed on the same lines as the cryo-maze using a radiofrequency power source instead of liquid nitrogen.

Concomitantly, a tricuspid valve annuloplasty was performed in 70 (37%) patients, aortic valve surgery was performed in 15 (8.0%), coronary artery bypass grafting was performed in 14 (7.5%), atrial septal defect closure was performed in 11 (5.9%), and LV restoration was performed in 3 (1.6%). LA reduction procedures were not performed.

Follow-up Examinations

All patients were contacted by telephone and during an outpatient clinic visit for follow-up examinations. A standardized questionnaire was used for symptomatic evaluations. Echocardiographic follow-up studies were generally performed at the National Cardiovascular Center at 1, 3, 5, 10, and 15 years after surgery, regardless of symptoms. Electrocardiograms were routinely performed at the outpatient clinic every 6 to 12 months regardless of symptoms and done immediately if a patient demonstrated any symptoms. Complete follow-up information was available for 182 (97.5%) patients because we lost contact with 5 during the follow-up period. The mean length of follow-up for the survivors was 7.4 ± 4.3 years, and 1400 hundred postoperative patient-years were available for analysis. The durability of mitral repair was primarily assessed by performance of a reoperation as well as by echocardiographic assessment. The durability of the maze procedure was assessed by electrocardiographic findings; other events briefly investigated included all-cause death, thromboembolism, bleeding, and endocarditis.

Postoperative Management

All patients were treated with warfarin sodium (Coumadin) postoperatively and the target international normalized ratio was basically between 2.0 to 3.0, which was modified owing to the patient's condition. Anticoagulation was continued until 3 or 6 months' time in the outpatient clinic, and it was discontinued if the electrocardiogram showed sinus rhythm and the patients did not feel palpitations. A Holter electrocardiographic study was examined in case the patient had palpitations with sinus rhythm.

Cardioversion was tried only during the hospital stay, by intravenous class Ia and/or class Ic antiarrhythmic agents with or without electrical cardioversion. An oral class Ia antiarrhythmic agent was continued for at most several months, only when an intravenous agent was effective. Beta-blocker was the basic strategy to maintain sinus rhythm, if applicable.

Data Analysis

Nonparametric, non-risk-adjusted estimates of freedom from events were obtained by the method of Kaplan and Meier. A paired *t* test was used to compare the degrees of LV diastolic and systolic diameters, fractional shortening, and peak tricuspid regurgitant pressure gradient. A univariate and multivariate Cox hazard regression analysis was used to identify predictors of survival and freedom from events. All values are expressed as the mean \pm standard deviation.

RESULTS

There were 2 (1.0%) operative deaths and 23 (12.3%) late deaths. Seven of the late deaths were of cardiac origin and included sudden death, and 2 were due to heart failure. The 5-, 10-, and 15-year survivals for the entire series were 94%, 82%, and 71% (Figure 1, A).

There were 20 (10.7%) readmissions for heart failure (NYHA class \geq III), and the rates of freedom from heart failure after 5, 10, and 15 years were 93%, 86%, and 79%, respectively (Figure 1, B). Eleven (5.9%) patients underwent a reoperation, for recurrence of MR in 7, hemolysis in 3, and endocarditis in 1. The rates of freedom from reoperation after 5, 10, and 15 years were 95%, 93%, and 91%, respectively (Figure 1, C). Hemolysis was the main cause of early failure of mitral repair; hemolysis resulting from partial detachment of the annuloplasty ring occurred in 2 patients and a regurgitant jet in 1. Echocardiographic follow-up examinations revealed moderate or severe MR (≥ 3) in 25 (13%) patients during the follow-up period, and the rates of freedom from MR were 98%, 91%, 86%, and 61% after 1, 5, 10, and 15 years, respectively (Figure 1, D). Univariate analysis showed that recurrence of MR of grade 3 or more was associated with preoperative large LA diameter (≥ 70 mm) and LV diastolic diameter (≥ 65 mm), as well as recurrence of AF (Table 2). Multivariate Cox hazard regression analysis revealed that a preoperative large value for LV diastolic diameter (≥ 65 mm) was the most significant risk factor for recurrence of MR of grade 3 or more. To determine the impact of LV size on MR recurrence, we determined the freedom rates in patients with a small LV (LV diastolic diameter < 65 mm, $n = 125$) and large LV (LV diastolic diameter ≥ 65 mm, $n = 62$) (Figure 1, E). The 10- and 15-year rates of freedom from MR of grade 3 or more for the group with a small LV were 91% and 69%, respectively, whereas

TABLE 1. Baseline patient characteristics

Variables	
Total patients, n (%)	187 (100%)
Male, n (%)	131 (70%)
Mean age, y (SD)	62 (11)
BSA, m ² (SD)	1.58 (0.17)
Hypertension, n (%)	46 (25)
Smoker, n (%)	37 (20)
Hyperlipidemia, n (%)	19 (10)
Diabetes mellitus, n (%)	16 (8.6)
<i>NYHA class</i>	
II, n (%)	101 (54)
III, n (%)	60 (32)
IV, n (%)	26 (14)
<i>Mitral leaflet prolapse</i>	
Anterior, n (%)	53 (28)
Posterior, n (%)	75 (40)
Both, n (%)	33 (18)
Nonprolapse etiology, n (%)	27 (14)
AF duration, y (SD)	3.5 (4.1)
AF duration >10 y, n (%)	15 (8.0)
f wave in V ₁ < 0.1 mV, n (%)	25 (19)
<i>Echocardiographic measures</i>	
LA diameter, mm (SD)	60 (12)
LA diameter >70 mm, n (%)	15 (8.0)
LVDd, mm (SD)	63 (4.6)
LVDs, mm (SD)	36 (8.5)
Fraction shortening, % (SD)	35 (8.4)
TRPG, mm Hg (SD)	35 (14)
<i>Procedures</i>	
<i>Mitral repair</i>	
Leaflet resection, n (%)	91 (49)
Chordal reconstruction, n (%)	69 (37)
Edge to edge repair, n (%)	30 (16)
Ring (band) annuloplasty, n (%)	156 (83)
<i>Maze procedure</i>	
Cryo-maze, n (%)	110 (59)
Cox/Kosakai maze, n (%)	69 (37)
Radiofrequency maze, n (%)	8 (4.3)

BSA, Body surface area; NYHA, New York Heart Association; AF, atrial fibrillation; SD, standard deviation; LA, left atrial; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; TRPG, peak tricuspid regurgitant pressure gradient.

those were 77% and 47%, respectively, for the group with a large LV. Type of MR and site of prolapse were not significant factors for long-term durability of the mitral repair (Table 2), nor was the type of repair, including lack of ring annuloplasty.

Functional follow-up echocardiographic examination showed that average LV diastolic diameter decreased from 63 to 49 mm after 1 year and to 47 mm after 15 years, changes that were statistically significant ($P < .01$ vs preoperative measurements) (Figure 2, A). The average LV systolic diameter decreased from 36 to 30 mm after 1 year (not significant) (Figure 2, A) and to 29 mm after 15 years ($P < .05$ vs preoperative measurements). The average fractional shortening

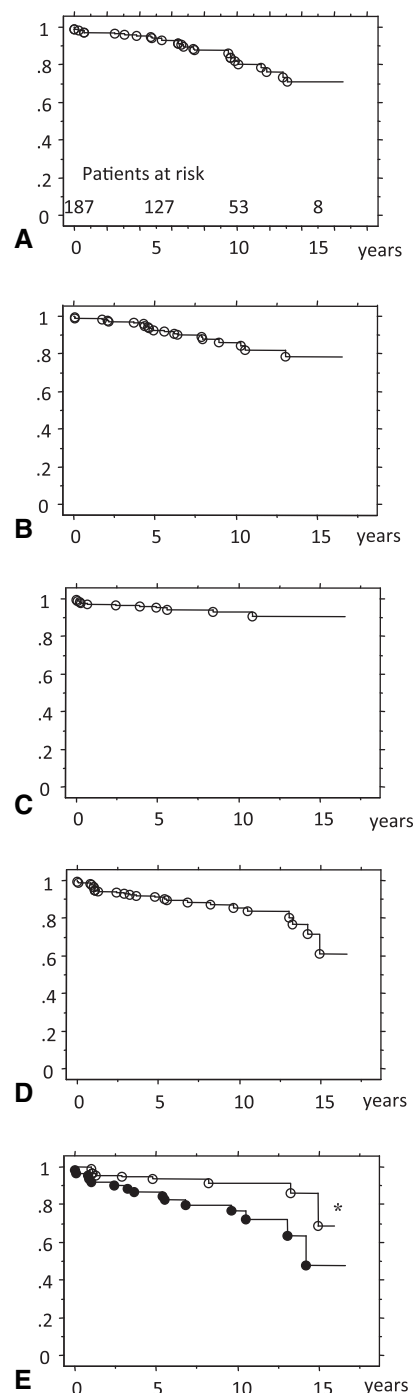


FIGURE 1. A, Actuarial survival after the operation. B, Rate of freedom from NYHA class III heart failure or greater. C, Rate of freedom from reoperation. D, Rate of freedom from greater than moderate (≥ 3) MR. E, Rates of freedom for small LV (line with white circle; LV diastolic diameter < 65 mm, n = 125) and large LV (line with black circle; LV diastolic diameter ≥ 65 mm, n = 62) groups. * $P < .01$.

was 35% preoperatively, then 34% after 1 year and 36% after 15 years (data not shown). Average peak tricuspid regurgitant pressure gradient also decreased from 35 to 25 mm Hg

TABLE 2. Predictors of recurrence of MR at grade greater than moderate (≥3): Univariate and multivariate analyses

Variables	Freedom from MR ≥3			
	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
NYHA (I, II)	0.48 (0.21–10.8)	.0747	—	—
Prolapse etiology	0.8 (0.27–2.34)	.685	—	—
Anterior prolapse	0.98 (0.45–2.15)	.951	—	—
Posterior prolapse	0.64 (0.29–1.41)	.2667	—	—
Both leaflets prolapse	0.64 (0.19–2.16)	.4766	—	—
Leaflet resection	0.54 (0.24–1.23)	.1437	—	—
Chordae reconstruction	1.29 (0.58–2.84)	.5292	—	—
Edge to edge repair	0.54 (0.13–2.28)	.3979	—	—
Ring annuloplasty	0.91 (0.31–1.84)	.5408	—	—
Recurrent AF rhythm	2.37 (1.09–5.33)	.0368	2.16 (0.92–5.1)	.0782
LV diastolic diameter ≥ 65 mm	2.86 (1.28–6.37)	.0102	2.63 (1.12–6.17)	.0268
LA diameter ≥ 70 mm	2.81 (1.05–7.5)	.0394	2.12(0.42–3.815)	.6847

MR, Mitral regurgitation; HR, hazard ratio; CI, confidence interval; NYHA, New York Heart Association; AF, atrial fibrillation; LV, left ventricular; LA, left atrial.

after 1 year, which was a significant difference ($P < .01$) (Figure 2, B), and was 26 mm Hg after 15 years.

Sinus rhythm was regained in 86% patients after 6 months and was present in 79%, 70%, and 63% after 5, 10, and 15

years, respectively (Figure 3, A). Univariate analysis showed that a non-cryo-maze procedure, long AF history (≥ 10 years), small voltage of f wave in V_1 (≤ 0.1 mV), and large LA diameter (≥ 70 mm) were significant risk factors for AF recurrence (Table 3). Multivariate Cox hazard regression analysis revealed that a small f-wave voltage in V_1 was the most significant risk factor for AF recurrence. Eleven (5.9%) thromboembolic episodes were detected in follow-up examinations (0.79%/patient-year) and 7 occurred in patients with recurrent AF rhythm (Figure 3, B).

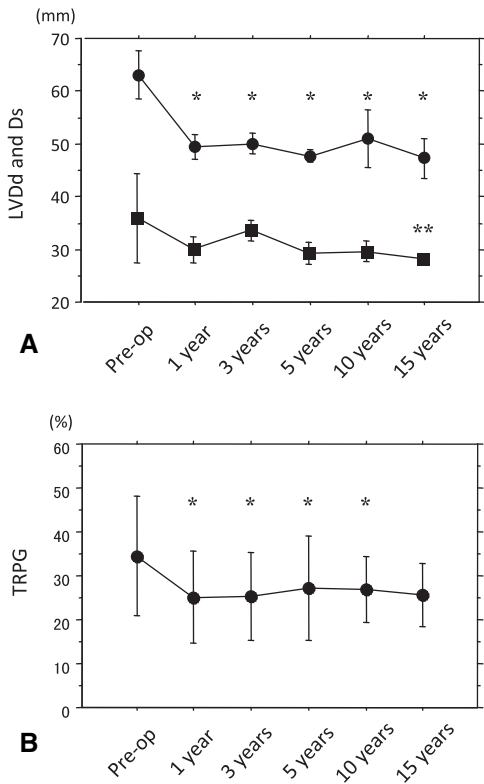


FIGURE 2. A, Left ventricular diastolic diameter (LVDd) and systolic diameter (Ds) preoperatively and 1, 3, 5, 10, and 15 years after the operation. * $P < .05$ versus preoperative LVDd. ** $P < .05$ versus preoperative LVDs. B, Peak tricuspid regurgitant pressure gradient (TRPG) preoperatively and 1, 3, 5, 10, and 15 years after the operation. * $P < .05$ versus preoperative TRPG.

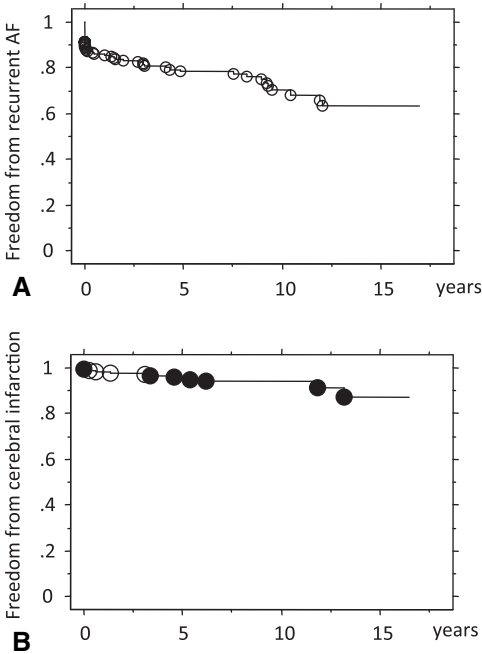


FIGURE 3. A, Rate of freedom from recurrence of atrial fibrillation (AF). B, Rate of freedom from cerebral infarction. Open circle, Cerebral infarction in patient with sinus rhythm. Closed circle, Cerebral infarction in patient with recurrent AF.

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TABLE 3. Predictors of recurrence of AF: Univariate and multivariate analyses

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Cryo-maze procedure	0.46 (0.25–0.86)	.0153	0.91 (0.451–1.81)	.7812
f wave in $V_1 < 0.1$ mV	19.3 (10.1–36.9)	<.0001	21.9 (10.0–47.9)	<.0001
AF duration >10 y	4.47 (2.2–9.05)	<.0001	1.56 (0.69–3.51)	.2819
LA diameter ≥ 70 mm	4.14 (1.98–8.66)	.0002	3.22 (1.42–7.27)	.005

AF, Atrial fibrillation; HR, hazard ratio; CI, confidence interval; LAD, left atrial.

DISCUSSION

In our previous report, we¹² analyzed the efficacy of a cryo-maze procedure for patients with AF who underwent mitral valve surgery, which showed that sinus conversion is likely to improve the rate of freedom from thromboembolic events and restore enlarged LV size. Furthermore, LA size, duration of AF, and f-wave voltage were found to be key factors related to a successful maze procedure. In the present study, we focused on long-term outcomes regarding accelerated functional and survival benefits after a maze procedure in addition to mitral repair. Although we applied 1-day Holter electrocardiographic monitoring only to patients with a history of palpitations, recent expert consensus recommends a 1- to 7-day Holter monitor study, a 4-week autotrigger event monitor, or mobile cardiac outpatient telemetry to identify asymptomatic recurrences of AF.¹³ Not only the method of the maze procedure but also the follow-up strategy should be adapted.

The success rate for the maze procedure was greater than 86% in our series of patients at 6 months' follow-up and the 5-year rate of freedom from recurrent AF was 79%, which are excellent rates when compared with other reports.¹⁴ The long-term results were also satisfactory, with 63% of this high-risk patient group free from recurrent AF after 15 years. The LA diameter was significantly reduced from an average 60 to 49 mm after the operation, although the LA became enlarged over time for an average LA diameter size of 55 mm after 15 years (data not shown). Re-expansion of the LA diameter may contribute to recurrence of AF.

Risk factors for AF recurrence in the present study were long AF history (≥ 10 years), small f-wave voltage in V_1 (≤ 0.1 mV), and large LA diameter (≥ 70 mm), as previously reported.¹⁵ Among those, a small f-wave voltage in V_1 was shown to be the most significant parameter, indicating that it is the key factor to determine whether to perform a maze procedure. Avoidance of a cryo-maze procedure such as a Cox or Kosakai procedure or ablation using an alternative energy source was also found to be significant. Although it is unclear whether performance of a cryo-maze procedure provided a better outcome, we speculated that a cut-and-sew technique might not reach the annulus adequately, and a radiofrequency technique may not apply ablation deep enough to the atrial wall. Therefore, combined with the cost benefit, we think that a cryo-maze procedure is the best

option. Furthermore, although the rate of freedom from cerebral infarction was satisfactory, 7 of 11 events occurred in patients with recurrent AF, emphasizing the importance of a successful maze procedure to avoid cerebral infarction.

Concerning postoperative survival, we analyzed the factors predictive of patient survival using a univariate Cox hazard regression analysis. We found no significant predictors for survival, such as preoperative NYHA class, mitral lesions, reconstruction procedure, preoperative LV or LA size, or postoperative sinus continuance. We speculated that the sample size may be too small to obtain the significant difference, because only 9 patients died of cardiac events including sudden death (including hospital deaths) among 187 patients.

As for valve and cardiac functions, the rates for survival and long-term freedom from heart failure (NYHA class \geq III) and reoperation were satisfactory, whereas our echocardiographic examinations found additional incidence of MR recurrence. The mitral repair improved cardiac function and accelerated reverse remodeling of the LV to downsize it postoperatively, and those improvements were well maintained for a number of years. The rate of freedom from recurrence of MR of grade 3 or more was excellent after 10 years, although it decreased to 61% after 15 years, even though the number of patients at risk was small. Unexpectedly, univariate analysis showed that posterior leaflet repair did not well suppress the recurrence rate of MR compared with anterior repair, contrary to what was described in other articles.^{3,16} This finding might be because of the earlier establishment of artificial chordal reconstruction for anterior repair in this study.⁸ However, further univariate and multivariate analyses revealed that a large LA and large LV are primary contributors to MR recurrence and that AF recurrence was also associated with MR recurrence, indicating common factors underlying recurrence of those conditions. Among them, LV dilatation was shown to be an independent risk factor for MR recurrence; thus, surgery before LV remodeling may be a key factor for long-term durability of mitral repair. Reverse LV remodeling has been shown to be associated with longer mitral repair durability in patients with advanced dilated cardiomyopathy or ischemic cardiomyopathy accompanied by MR.^{17,18} Among patients with cardiomyopathy in whom the LV is severely dilated, some show echocardiographic evidence of reverse LV

remodeling early or late after surgery, whereas others show a persistent or progressing remodeling pattern despite a successful initial mitral repair.¹⁹⁻²² In combination with these, reverse remodeling is a key factor for the long-term durability of mitral repair, which may help reverse remodeling in some cases, although in others it may not help downsize the heart. Therefore, early indications of surgery before remodeling of the LV can contribute to the long-term durability of mitral repair. Although valve replacement may be considered instead of repair from the perspective of high recurrence rate of MR in patients with a large LV, we still recommend valve repair, which showed excellent rates of long-term freedom from heart failure, reoperation, and cerebral infarction. Mitral repair in combination with a maze procedure certainly confers good quality of life (Figure 1, B and C, and Figure 3, B).

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